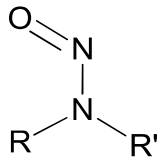
CHAPTER-1

N-Nitrosamines & *N*-Nitrosamides: Introduction, Synthesis and Applications

1.1 Introduction

N-Nitroso compounds are chemically represented as $R_2N–N=O$ (**I**) where NO (nitrosyl group) is directly linked to amine *via* N-N single bond. These are synthesized from the reaction of secondary amines/amides with nitrosyl cation (NO^+). *N*-Nitrosamines were first reported by Geuther in 1863. In 1954, Magee and Barnes reported that dimethylnitrosoamine produced liver cancer in animals. Later, Magee and Barnes (1967) and Druckrey *et al*. (1967) found that *N*-NO containing compounds induce a wide variety of tumours in rats and many other living species, including monkeys [1]. Hence, *N*-nitrosamines are generally known as carcinogenic and mutagenic compounds [2].



I

N-Nitroso compounds and their derivatives occur in a wide range of foods, natural products, fluids, rubber additives, agricultural chemicals, tobacco, detergents, rust solvents, plastics, leather products, textiles, cosmetics and drugs [3]. They are occasionally used as solvents or synthetic intermediates in organic chemistry and act as directing group for inert C-H bond activation to give *ortho*-functionalized aniline compounds. Also, 1,1-dimethylhydrazine obtained from *N*-nitroso-dimethylamine (NDMA) is used as the rocket fuel [4]. Hence, *N*-nitroso compounds display wide applications in different fields.

1.2 Structure of *N*-nitroso compounds

The N-nitroso compounds can be divided into two classes: *N*-nitrosamines and *N*-nitrosamides. *N*-nitrosamines are the *N*-nitroso derivatives of secondary amines (Figure

1.1 A) while *N*-nitrosamide and its related compounds are those of substituted amides, ureas, carbamates, guanidines, and similar compounds (Figure 1.1 B) [5].

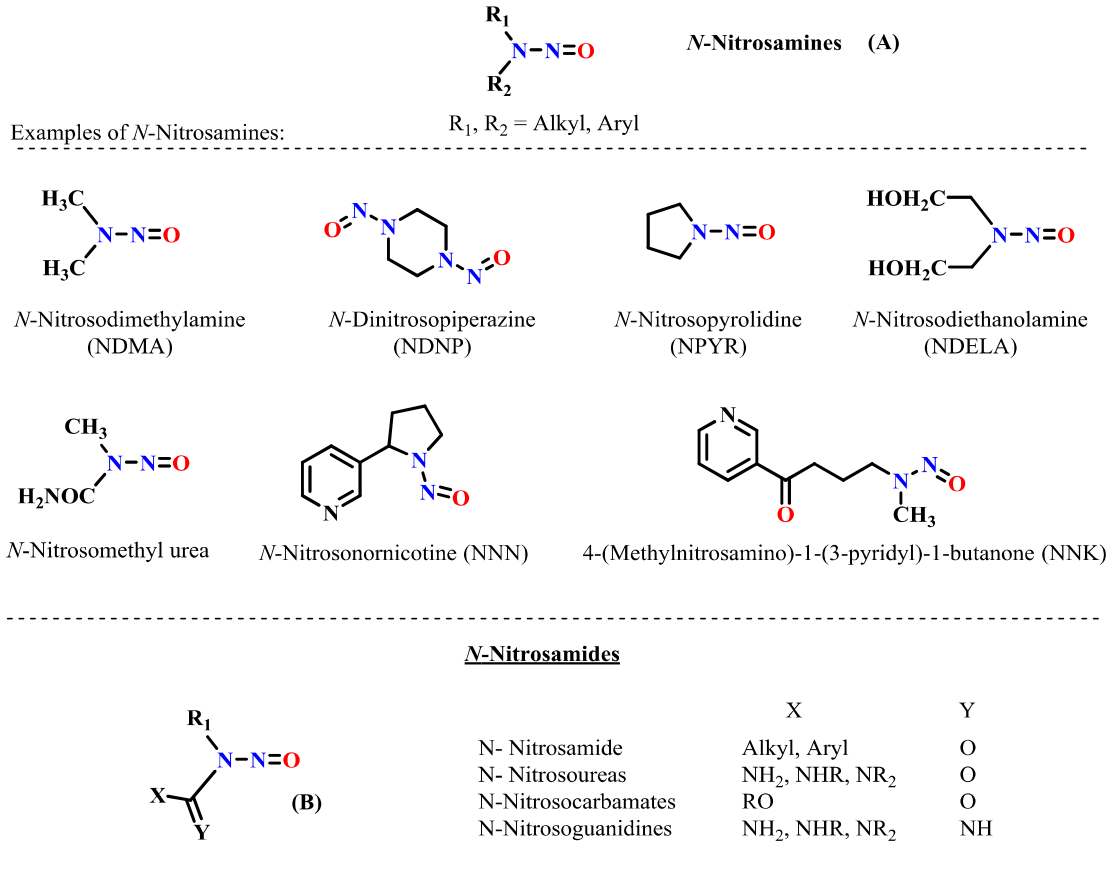


Figure 1.1 Some examples of nitrosamines and nitrosamides

1.3 Physical organic properties of *N*-nitrosamines and their reactivity

Alky nitrosamines are usually yellow or yellow-green and white in colour whereas aromatic nitrosamines appear as yellow or reddish-yellow colour. In general, both *N*-nitrosamines exist in liquid form as well as solid form with different boiling and melting points. The solid nitrosamines are found to be more stable when compared with liquid ones. Substituents on the amine nitrogen play an important role in the stability of the compound attached. On the other hand, temperature as well as pH also significantly affects the stability. They are stable in the dark, in neutral or alkaline solution but are

less stable in more acidic solutions or in light. They are partially soluble in water but soluble in common organic solvents such as alcohols and halogenated hydrocarbons. The densities of the majority of nitrosamines are usually in the range 0.9 to 1.2 gcm^{-3}. All *N*-nitrosamines exhibit three relatively intense bands in the infrared spectra. From which the two absorption bands in ranges 1410 to 1350 cm^{-1} and 1320 to 1160 cm^{-1} corresponds to N-N vibrations whereas the band 1095 to 1045 cm^{-1} corresponds to N=O stretching.

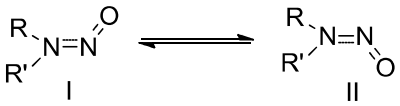


Figure 1.2 Restricted rotation of *N*-nitrosamines.

The nitrosamine (N-N=O) exists in two isomers which is also known as rotamers, i.e., *syn* and *anti.* It is because of the delocalization of lone-pair on nitrogen atom with N=O bond in *N*-nitrosamines. These two isomers can be easily detected, identified and distinguished through ^{1}H and ^{13}C NMR spectroscopy (Figure 1.2).

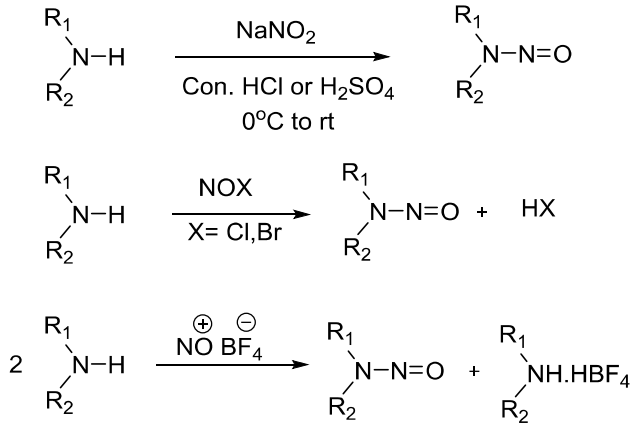
1.4 Synthesis of *N*-nitrosamines and *N*-nitrosamides

1.4.1 Synthesis of *N*-nitrosamines

The syntheses of *N*-nitrosamines are well-established reactions in organic chemistry. The classical method of *N*-nitrosamine preparation involves the use of nitrous acid generated (*in situ*) from sodium nitrite and concentrated mineral acid (*e.g.* HCl, H_2SO_4) [6]. Besides this traditional approach, other reagents such as nitrosyl chloride [7], nitrogen oxides (*e.g.* N_2O_3, N_2O_4, *etc*) [8], nitrosonium tetrafluoroborate [9] and fremy's salt [10] were used for the preparation of various *N*-nitroso compounds from secondary amines.

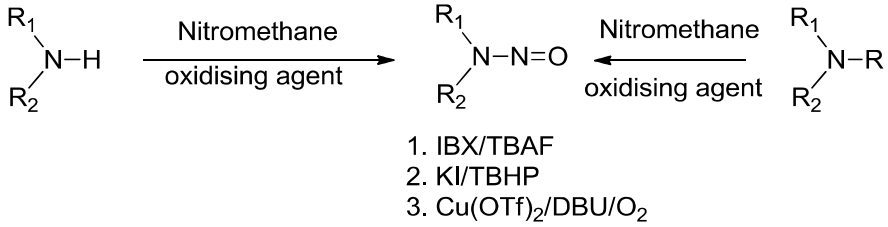
Besides, various heterogeneous reagents have been developed with combination of sodium nitrite or nitrogen oxide with different solid supports [11]. The major

limitations of these reagents are the use of strong acidic medium, reagents that are difficult to handle and store, harsh reaction conditions, etc.



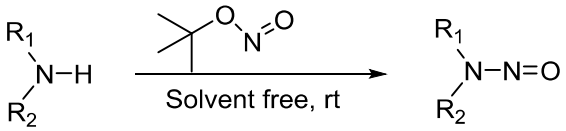
Scheme 1.1 Synthesis of *N*-nitrosamines with different reagent

Very recently, nitromethane (CH_3NO_2) has been used as an alternative source for generating the nitrosyl (NO) moiety. Nitromethane mediated *N*-nitrosation of secondary and tertiary amines in the presence of oxidizing agents such as IBX/TBAF [12], KI/TBHP [13] and $Cu(OTf)_2$/DBU/O_2 [14] have been established.



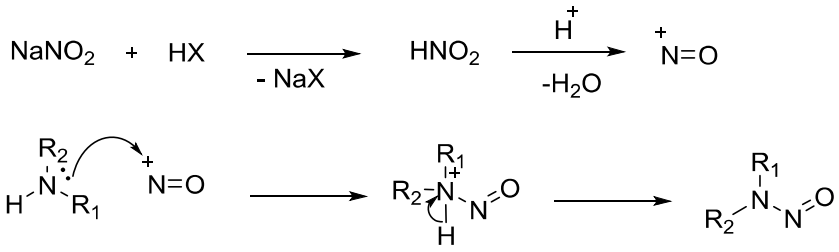
Scheme 1.2 Synthesis of *N*-nitrosamines using nitromethane

Last few years, our research group has focused on the chemistry of *N*-nitrosamines and recently we demonstrated *N*-nitrosation of various aryl, alkyl and benzylic secondary amines using *tert*-butyl nitrite under solvent free conditions [15].



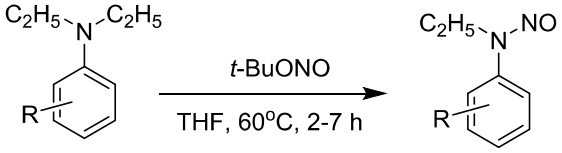
Scheme 1.3 Synthesis of *N*-nitrosamines with TBN

Typically, *N*-nitrosation of secondary amines is achieved using sodium nitrite and aqueous hydrochloric acid or H_2SO_4 which generates the nitrosonium ion [6] (Scheme 1.4). When nitrosonium cation reacts with primary amine, it undergoes diazotisation reaction while alkyl tertiary amines do not react. On the other hand, aromatic tertiary amines proceed for the ring nitrosation/nitration.



Scheme 1.4 Generation of nitrosonium ion and it's reaction with secondary amines

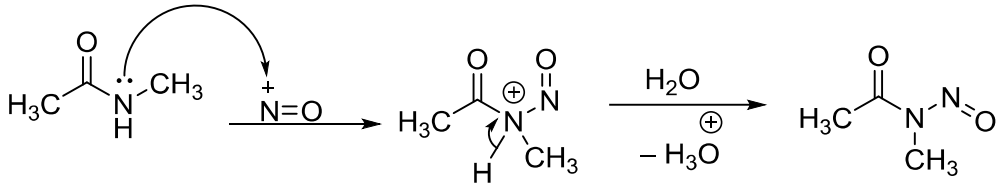
Furthermore, a dealkylative *N*-nitrosation of *tert*-amines was successfully achieved under mild conditions. For instance, dealkylative *N*-nitrosation of *N,N*-dialkylaniline derivatives has been achieved with the help of *tert*-butyl nitrite under mild reaction conditions [16] (Scheme 1.5).



Scheme 1.5 Dealkylative *N*-nitrosation of diethyl aniline using *tert*-butyl nitrite

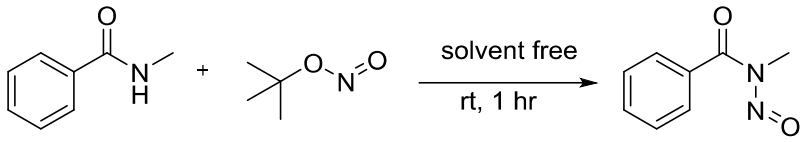
1.4.2 Synthesis of *N*-nitrosamides

N-Nitrosamides are much less stable than the parent *N*-nitrosamines. *N*-nitrosoamide is an important intermediate in organic synthesis. *N*-nitrosamides can be prepared from *N*-monosubstituted carboxamides in the presence of the nitrosyl cation [17] (Scheme 1.6).



Scheme 1.6 Reactions of amide with nitrosonium ion

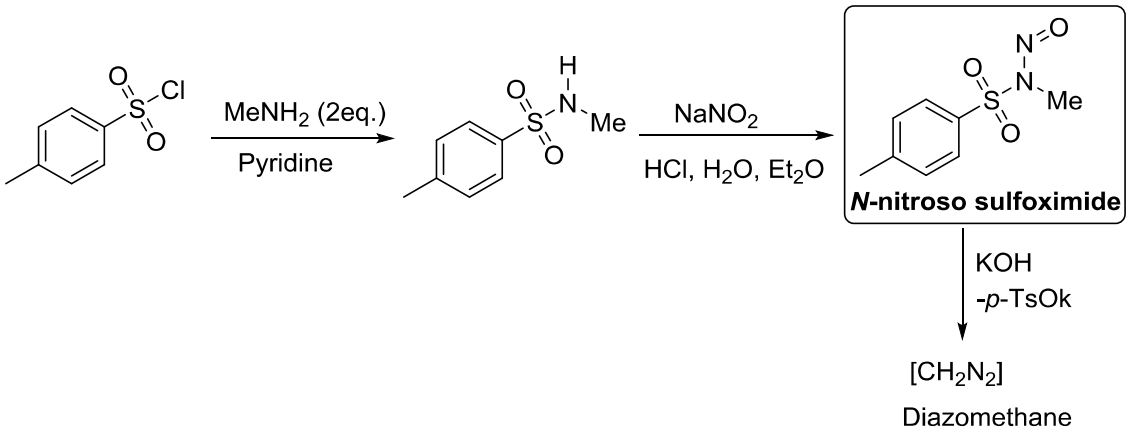
tert-Butyl nitrite (TBN) used as a multitasking reagent for the controlled synthesis of *N*-nitrosoamide from *N*-alkyl amides, Recently, *tert*-butyl nitrite (TBN) promoted nitrosylation of secondary amides under solvent-free conditions at room temperature has been reported (Scheme 1.7).



Scheme 1.7 Synthesis of *N*-nitroso amide with TBN

1.4.3 Synthesis of *N*-nitroso sulfoximide compound

N-nitroso sulfoximide is another type of *N*-nitroso amide, has been widely used as a precursor for the preparation of diazomethane. *N*-methyl-*N*-nitrosobenzenesulfonamide is prepared from *p*-toluenesulfonyl chloride as shown in Scheme 1.8 [18].



Scheme 1.8 Synthesis of *N*-nitroso sulfoximide

1.5 Biological applications of *N*-nitrosamines and *N*-nitrosamides

N-Nitroso compounds have wide applications in medicinal chemistry. Generally, these compounds are used in various medical treatments including cancer, cardiovascular diseases, diabetic agent, central nervous system related to immunity and physiological disorders (Figure 1.3) [1,2]. Cyclic *N*-nitrosamines **A** and **B** have been used in treatment of cardiovascular disease, which inhibit the blood clotting in the blood vessel

of mammals [3]. *N*-Nitroso-*N*-cyclohexylhydroxylamine **C** has been used as a synergistic agent that increases the insecticidal activity of chlordane. One of the *N*-nitrosoaniline derivatives, dephostatin **D** is a potential inhibitor of cysteine-containing enzymes such as tyrosine and papain [19]. *N*-Methyl-*N*-nitrosourea and its derivatives were found to be powerful antitumor agents [20]. For example, carmustine **E** is widely used as alkylating agent in chemotherapy [21]. Similarly, dopastin **F** is used as an antihypertensive agent that inhibits the copper-dependent dopamine *β*-hydroxylase efficiently [22]. Also, nitrosourea such as *N, N′*-bis (2-chloroethyl) nitrosourea (**G**) and lomustine (**H**) has been used in chemotherapy. *N*-Nitroso L-proline **I** (NPRO) was detected in stomach and being studied for its clinical applications [23]. Detailed biological activities of some important compounds are discussed below.

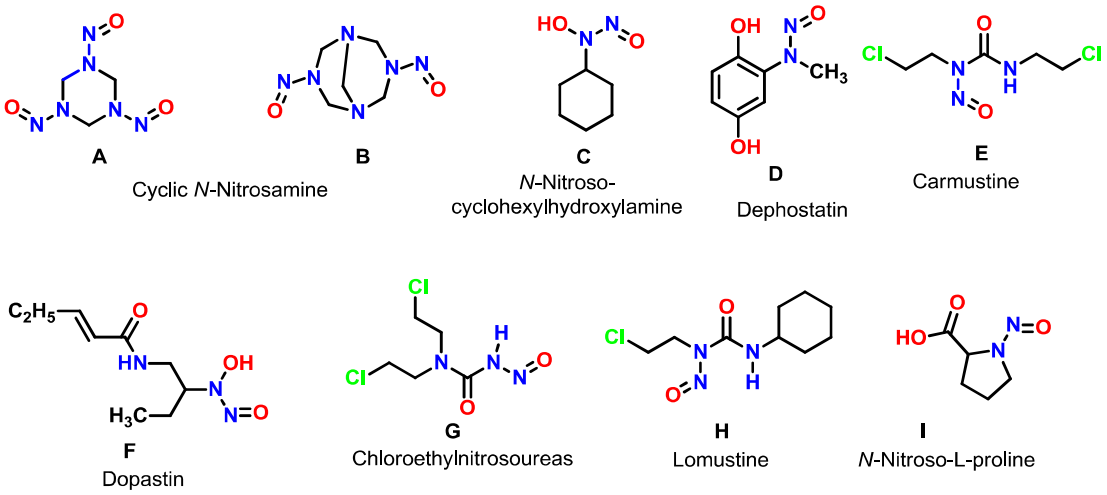


Figure 1.3 Biologically important *N*-nitroso compounds

15.1 Dephostatin

Dephostatin is a tyrosine phosphatase inhibitor which was isolated from the culture broth of *Streptomyces* sp. MJ742-NF5. Dephostatin is also known as an antibiotic which acts on gastrointestinal bacterias which are resistant to luoroquinolone and cephalosporin antibiotic. Dephostatin disrupts signaling throughboth the SsrA-SsrB and PmrB-PmrA two-component regulatory systems and restores sensitivity to the last-

resort antibiotic, colistin. Cell-based experiments and mouse models of infection demonstrate that dephostatin attenuates Salmonellavirulencein vitroandin vivo, suggesting that perturbing regulatory networks is apromising strategy for the development of anti-infective.

1.5.2 Carmustine

Carmustine, sold under the brand name BiCNU among others, is a medication used mainly for chemotherapy. It is a nitrogen mustard β-chloro-nitrosourea compound used as an alkylating agent. As an alkylating agent, carmustine can form interstrand crosslinks in DNA, which prevents DNA replication and DNA transcription

1.5.3 Dopastin

Dopastin is a chemical compound produced by the bacteria Pseudomonas No. BAC-125. It was first isolated and characterized in 1972. It is an inhibitor of the enzyme dopamine β-hydroxylase. The total synthesis of dopastin was completed in 8 steps starting from l-valinol. N-Nitrosohydroxylamino function was introduced through an oxaziran with retention of the absolute configuration in the final product. Thus, the 2S-configuration of dopastin was proved by the total synthesis. Racemic dopastin was also synthesized from isobutyraldehyde in 7 steps.

1.5.4 Lomustine

Lomustine is an alkylating agent used as a part of chemotherapeutic regimens for the treatment of primary and metastatic brain tumors as well as refractory or relapsed Hodgkin's disease in addition to surgical and/or radiotherapeutic treatments.

1.6 Synthetic applications of *N*-nitrosamine in organic chemistry

N-Nitrosamines are widely used in synthetic organic chemistry as precursor or valuable intermediates (Figure 1.4). Preparations of biologically important α-disubstituted hydrazines and mesoionic-heterocyclic compound sydnones are the

traditional applications of *N*-nitrosamines. These compounds undergo many reactions including oxidation, reduction, rearrangement, cyclization, denitrosation, photochemical reactions, etc. Some transformations involving nitrosamine is discussed below.

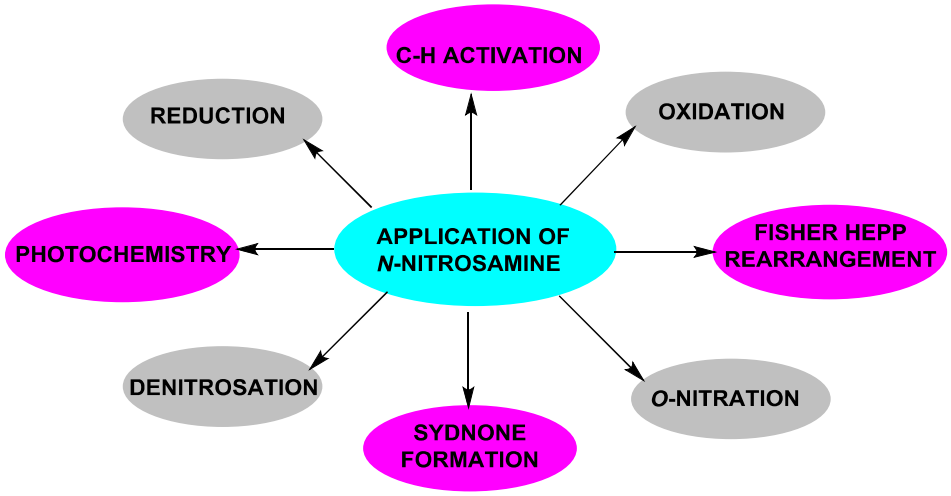


Figure 1.4 Synthetic applications of *N*-nitrosamines

1.6.1 Hydrazine synthesis

Hydrazines are N–N bond containing organic compounds exhibiting a wide range of biological properties including antibacterial, analgesic, anti-inflammatory, and antitumour activities (Fig. 1.5) [24]. Aryl hydrazines are versatile intermediates and frequently used as starting materials in organic synthesis including preparation of various bioactive heterocyclic compounds such as indoles, benzimidazoles, pyrazoles, indazoles, etc [25].

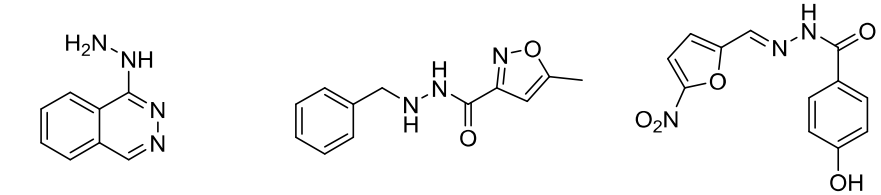
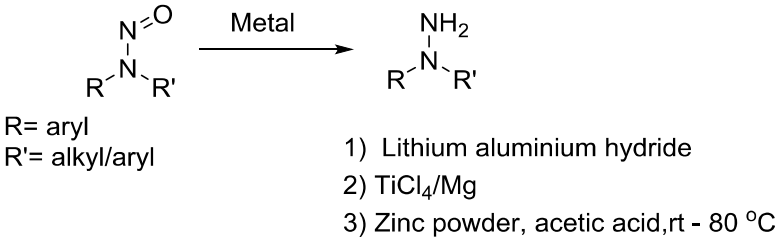


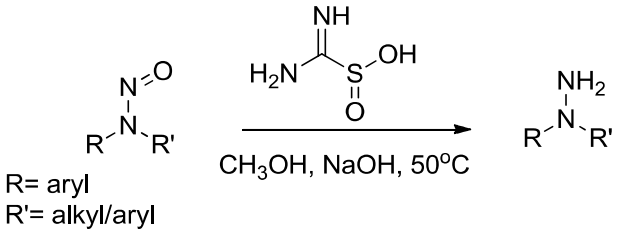
Figure 1.5 Hydrazine-based biological active pharmaceutical agents

Reduction of *N*-nitrosamine gives the corresponding hydrazine (Scheme 1.9). Frequently used metal based reducing agents are lithium aluminium hydride ($LiAlH_4$) [26], low valent titanium reagent ($TiCl_4$/Mg) [27] and zinc–acetic acid (Zn/AcOH) [28]. These reagents are highly sensitive to air and moisture which requires anhydrous solvents and an inert atmosphere.



Scheme 1.9 Reduction of *N*-nitrosamines in the presence of metal

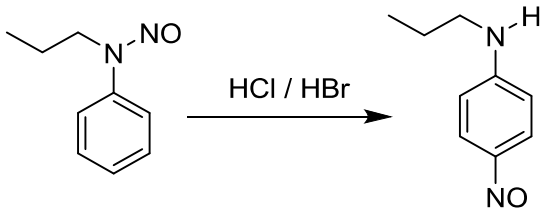
Recently, an efficient and green method has been reported for the reduction of aryl-*N*-nitrosamines into the corresponding hydrazine using thiourea dioxide under metal free condition in an aqueous medium (Scheme 1.10) [29].



Scheme 1.10 Reduction of *N*-nitrosamines using TDO

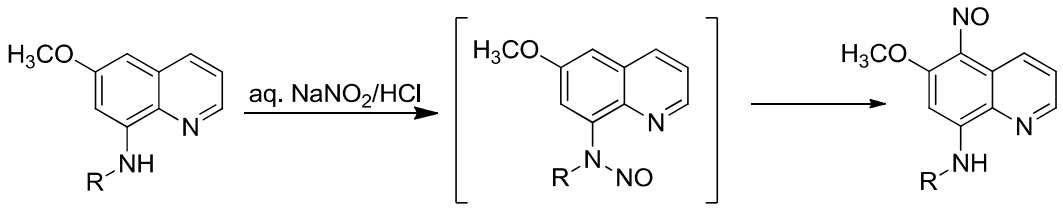
1.6.2 Fisher-Hepp rearrangement

Conversion of *N*-nitroso aromatic amines into *para*-nitroso aromatic amines in the presence of hydrochloric or hydrobromic acid is called Fisher-Hepp rearrangement (Scheme 1.11) [30]. Fischer-Hepp rearrangement was reported in 1886.



Scheme 1.11 Fischer-Hepp rearrangement

Fischer-Hepp rearrangement is an important reaction for the synthesis of *p*-nitroso aryl amines. Quinoline derivatives in the presence of aqueous sodium nitrite and HCl, undergo rearrangement to form *C*-nitrosamines *via* *N*-nitroso intermediates (Scheme 1.12) [31].



Scheme 1.12 Synthesis of *C*-nitroso quinoline derivative

1.6.3 *N*-Nitroso directed C-H activation reactions

The formation of a carbon-carbon or carbon-heteroatom bond by breaking high energy C-H bonds is generally difficult in organic synthesis. However, regioselective C-H functionalization has been achieved using transition metal catalysts which coordinate better with the substrate at a specific site in the presence of a directing group. In this context, *N*-nitroso groups have been well explored as a directing group in different C-H activation reactions due to their efficient binding with transition metals like palladium, rhodium, ruthenium, etc. to form metal nitroso complex as shown in Figure 1.5 [32].

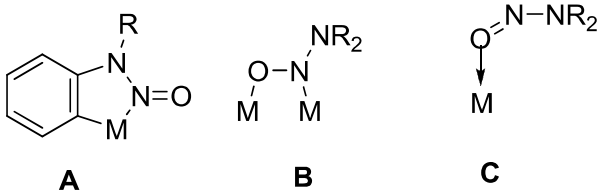
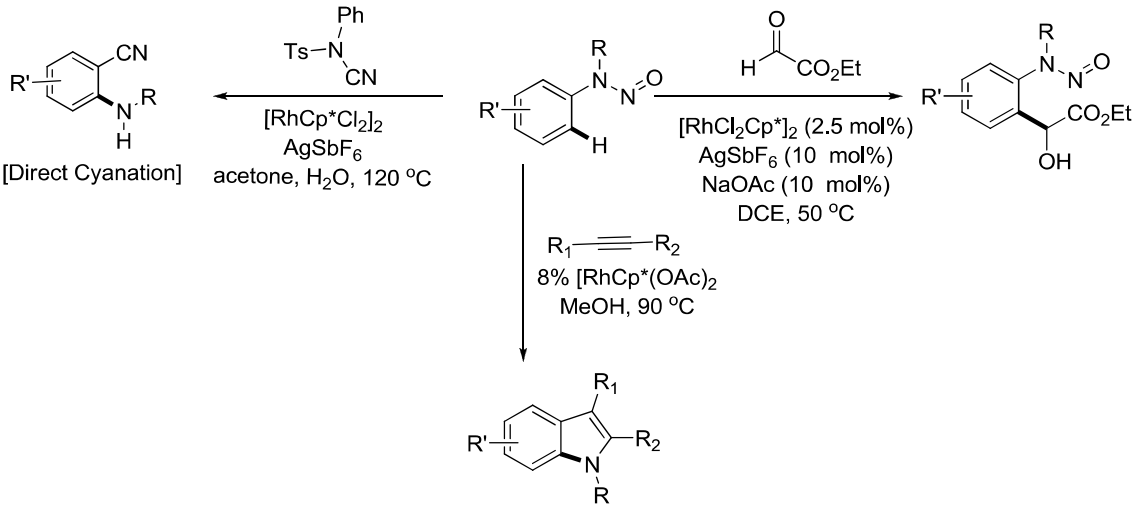


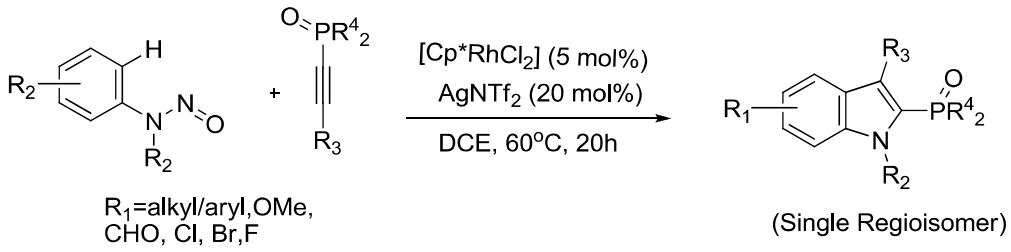
Figure 1.6 Binding modes of metal-nitrosamine

The synthesis of functionalized indoles was described by Wang *et al.* in 2013 through C-H annulations of *N*-alkyl *N*-nitrosoaniline in presence of rhodium catalyst at 90 °C temperature where *N*-nitroso group worked both as a directing group and an internal oxidant (Scheme 1.13) [33]. After that, Chen *et al*. reported Rh (III)-catalysed synthesis of 3-hydroxy-2-oxindoles with the help of *N*-nitroso directed C-H addition to ethyl 2-oxoacetate [34]. Later, *ortho*-cyanation of *N*-alkyl *N*-nitroso arylamines was achieved using *N*-cyano-*N*-phenyl-*p*-methyl benzenesulfonamide (NCTS) as cyanide source in the presence of Rh catalyst [35].

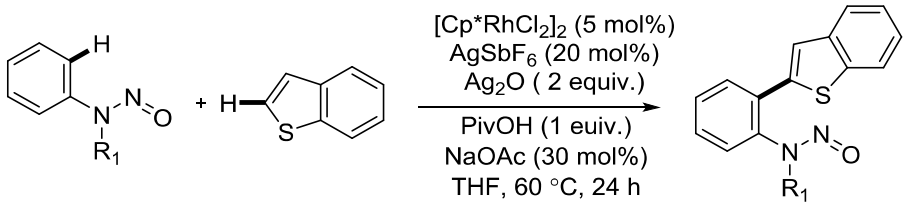


Scheme 1.13 Rhodium catalyzed *N*-nitroso directed C-H activation

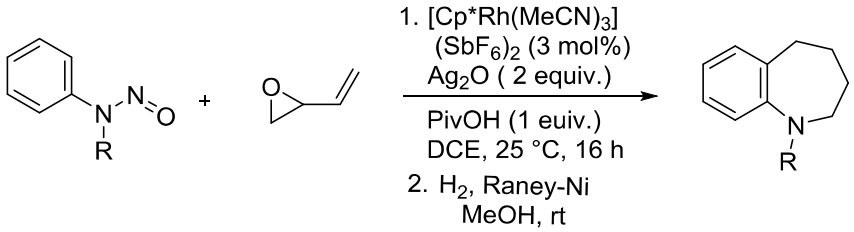
2-phosphorylate indoles were synthesised *via* Rh (III)-catalyzed redox-neutral C–H bond activation of *N*-nitrosoanilines with 1-alkynylphosphine oxides. This protocol was proficient in providing 2-phosphinoylindoles in excellent yield with good regioselectivity and functional group tolerance (Scheme 1.14) [36]. *N*-nitroso group directed mild oxidative C–H/C–H cross coupling of aniline with heteroarene was demonstrated (Scheme 1.15) by Wang *et al*. in 2018 [37]. Similarly, *N*-nitroso group directed synthesis of benzoazepane was achieved in good yields (Scheme 1.16) [38].



Scheme 1.14 Rh catalyzed synthesis of phosphinoylindole

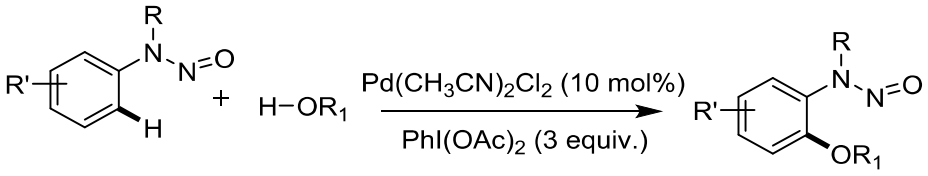


Scheme 1.15 *N*-Nitroso group enabled mild oxidative C–H/C–H cross coupling of aniline with heteroarene

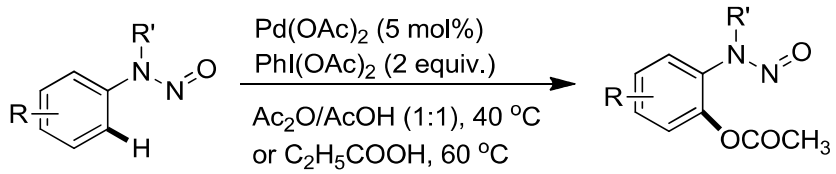


Scheme 1.16 Synthesis of benzoazepane

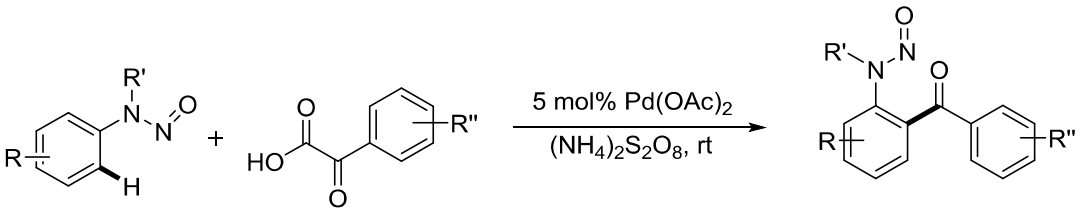
Palladium catalysed *N*-nitroso directed C-C bond forming reactions were also explored in the literature. For instance, Gao *et al*., described the *o*-alkoxylation of nitrosamines with alcohol and diacetoxy iodobenzene [$PhI(OAc)_2$] in the presence of palladium catalysts (Scheme 1.17) [39]. Recently, palladium-catalyzed *o*-acyloxylation of *N*-nitroso anilines with Ac_2O and acetic acid was reported (Scheme 1.18) [40]. Palladium catalysed decarboxylative *o*-acylation of *N*-nitrosoanilines was done using α-oxocarboxylic acids in presence of ammonium persulfate (Scheme 1.19) [41].



Scheme 1.17 *o*-alkoxylation of *N*-nitrosamines



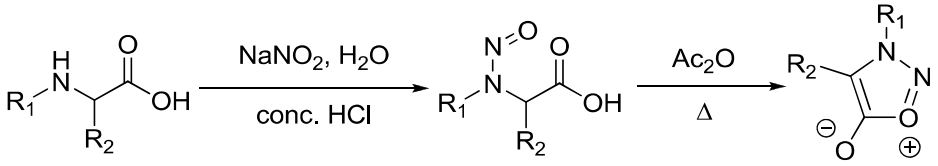
Scheme 1.18 Palladium catalyzed *o*-acyloxylation of *N*-nitrosoanilines



Scheme 1.19 Palladium catalyzed nitroso-directed *ortho*-acylation

1.6.4 Synthesis of sydnones

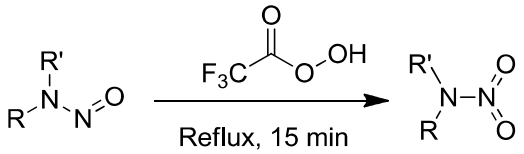
Sydnones are basically five-membered pseudo-aromatic heterocyclic molecules. 1,2,3-oxadiazole forms the main skeleton of sydnone. The molecule has delocalized balanced positive and negative charges along with its aromaticity and high lipophilicity. Sydnones are mesoionic heterocyclic compounds with several biological properties such as antibacterial, anti-inflammatory and antineoplastic agents [42] due to which they have received significant interest in chemistry. Sydnones are generally prepared by the reaction of secondary amino acids with sodium nitrite and hydrochloric acid in the presence of acetic anhydride (Scheme 1.20) [43].



Scheme 1.20 Classical method for preparation of Sydnones

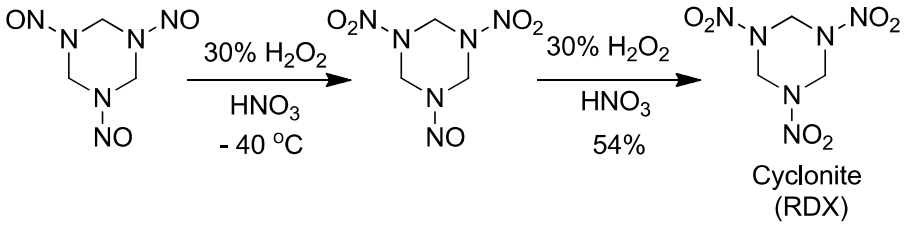
1.6.5 Synthesis of *N*-nitro amines from *N*-nitrosamines *via* oxidation

N-Nitroamines are prepared through the oxidation of *N*-nitrosamines in the presence of different oxidizing agents such as hydrogen peroxide with nitric acid, nitric acid and ammonium persulfate, and trifluoroperacetic acid. Among these methods, trifluoroperacetic acid was found to be most efficient for oxidising *N*-nitrosamine to *N*-nitramine due to high purity of products in quantitative yield (Scheme 1.21) [44].



Scheme 1.21 Oxidation of *N*-nitrosamines with trifluoroperacetic acid

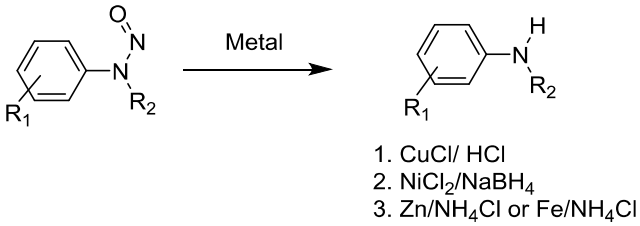
Oxidation of 1,3,5-trinitroso-1,3,5-triazacyclohexane using hydrogen peroxide (30%) and nitric acid (99%) gives 1,3,5-trinitro-1,3,5-triazacyclohexane (RDX) which is a powerful explosive (Scheme 1.22) [45].



Scheme 1.22 Oxidation of *N*-nitrosamines with hydrogen peroxide and nitric acid

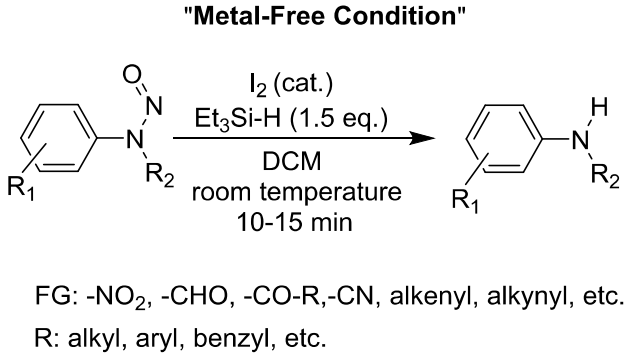
1.6.6 Denitrosation of *N*-nitroso amines

In organic synthesis, *N*-nitrosamines have been used not only as synthetic intermediates but also used as masking groups and directing groups. In this context, denitrosation of *N*-nitrosamines is considered to be an important reaction in organic synthesis. Formerly, denitrosation of *N*-nitrosamines was explored with metal based reducing agents such as CuCl/HCl [46], $NiCl_2/NaBH_4$ [47], Zn/NH_4Cl [48] and Fe/NH_4Cl [49] (Scheme 1.23).



Scheme 1.23 Reductive denitrosation of *N*-nitrosamines

Recently, a simple and green method for the denitrosation of aryl *N*-nitrosamines to anilines is reported under metal-free conditions using iodine and triethylsilane (Scheme 1.24) [50]. Triethylsilane is a mild and selective reducing agent used in combination with different metals or Lewis acids for the reduction of selected functional groups. In this condition, various reduction susceptible functional groups such as alkene, alkyne, nitrile, nitro, aldehyde, ketone and ester were found to be stable.



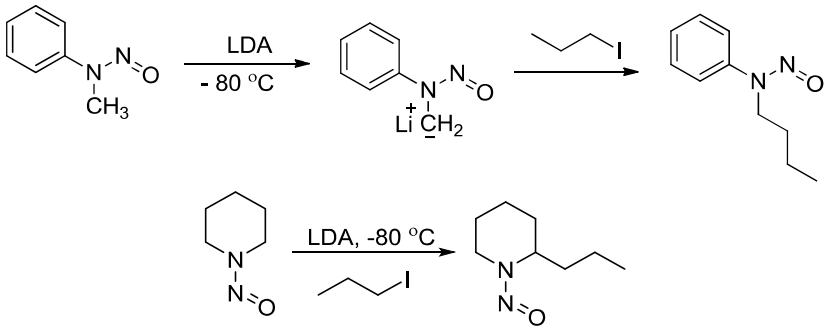
Scheme 1.24 Denitrosation of *N*-nitrosamines

1.7 *N*-Nitrosamines as masking groups

1.7.1 *N*-Alkylation of *α*-carbon of *N*-nitrosamine

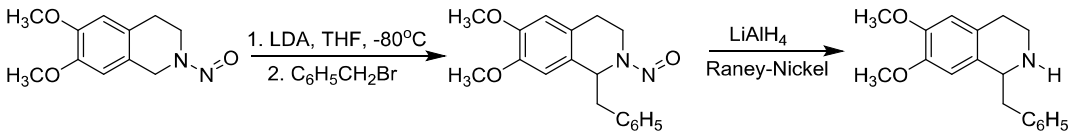
N-Nitrosamine is also used as a masking group in organic synthesis. The functionalization of *α*-carbon of secondary amine is difficult due to the presence of adjacent nitrogen atom. In this context, *N*-nitrosation facilitates the formation of carbanion with strong base such as *n*-BuLi and LDA. This lithiated compound undergoes electrophilic substitution with various electrophiles and provides valuable

synthetic intermediates. For example, *N*-nitroso *N*-butylaniline was prepared from *N*-nitroso *N*-methylaniline using lithium diisopropylamide (LDA) and iodopropane (Scheme 1.25) [51].



Scheme 1.25 Alkylation of *N*-nitrosamine through *α*-lithiation

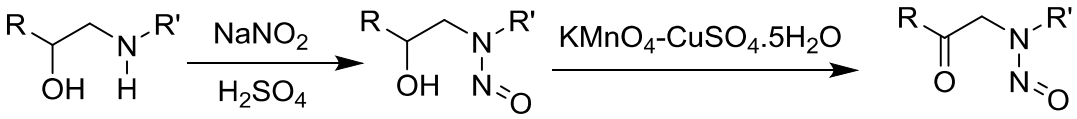
Similarly, the C-C bond formation reaction with lithiated nitrosamine followed by denitrosation *via* sequential reduction with lithium aluminium hydride and raney-nickel, was also demonstrated (Scheme 1.26) [53].



Scheme 1.26 Electrophilic substitution at *α*-carbon of *N*-nitrosamine

1.7.2 Oxidation of *β*-hydroxynitrosamines

N-Nitrosamines are also used as the masking group during the oxidation of *β*-hydroxyamines as shown in scheme 1.27 [53]. The oxidation was performed using the powdered potassium permanganate in DCM or benzene solvent.



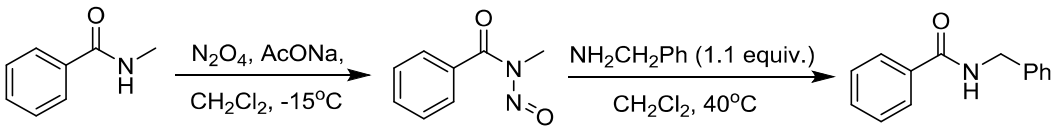
Scheme 1.27 Synthesis of *β*-ketonitrosamines

1.8 Applications of *N*-nitrosamides

N-Nitrosamides are less stable than *N*-nitrosamines and can get decomposed by thermal, photolytic or acid and base (nucleophilic) catalyzed pathways. Hence, unlike *N*-nitrosamines, the synthetic applications of *N*-nitrosamides are limited in the literature.

1.8.1 Transamidation of amide *via N*-nitrosamides intermediate

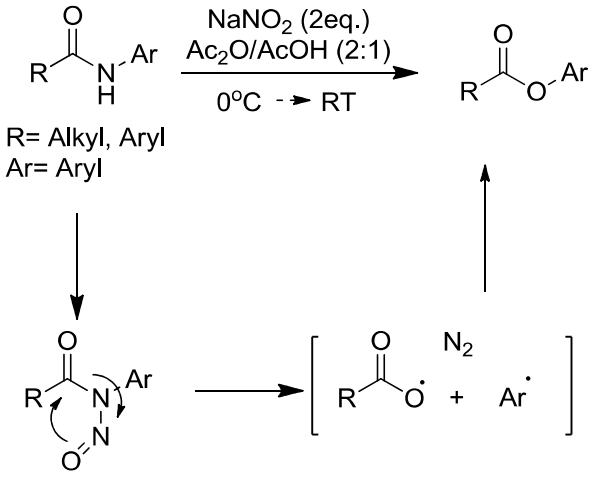
Amides are key functional groups that exist in many biomolecules, natural products, drugs, etc [54]. Transamidation is a chemical reaction in which an amide reacts with an external amine to generate a new amide. Transamidation of secondary amides are more challenging task in organic chemistry due to high stability of amide bond. In this context, *N*-nitrosamides have been used as the intermediates in transamidation reactions. *N*-methylbenzamide is firstly converted into *N*-nitroso-*N*-methylbenzamide in the presence of a nitrosating reagent, followed by nucleophilic substitution with an external amine to obtain desired amides (scheme 1.28) [55].



Scheme 1.28 Transamidation of secondary amides *via N*-nitrosamide

1.8.2 Conversion of *N*-aromatic amides to *O*-aromatic esters

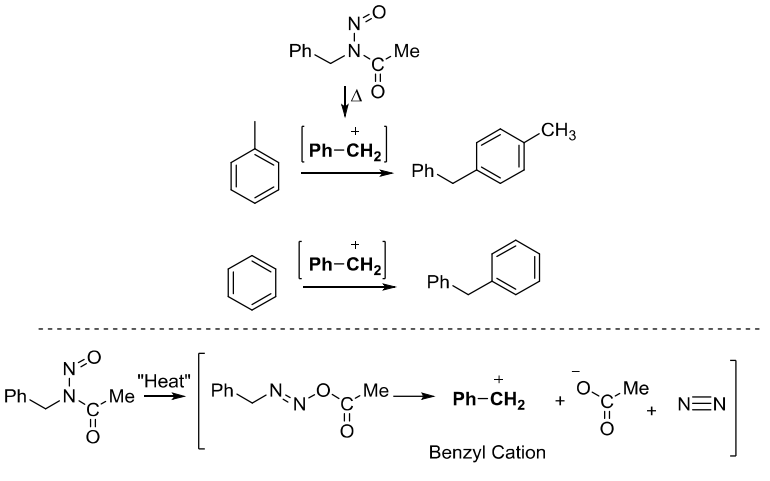
N-Aromatic secondary amides have been converted into *O*-aromatic esters *via N*-nitrosamide intermediate as shown in (scheme 1.29) [56]. The mechanism of the reaction involves radical formation and recombination. This method is inexpensive, convenient and does not require isolation of intermediate *N*-nitrosamides or diazonium salts.



Scheme 1.29 Formation of *O*-aromatic esters *via N*-nitrosamide

1.8.3 *N*-Nitrosoamide mediated Friedel-Crafts benzylation reaction

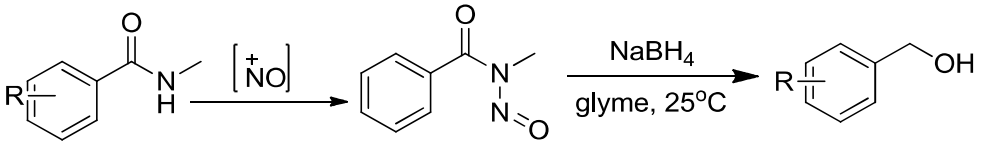
Friedel-Crafts alkylations involve aromatic substitution by an electrophile generally derived from some combination of an alkyl group and the conjugate base of a strong acid. ***N*-**Benzyl-*N*-nitrosoamide was used as benzyl (alkyl) source in Friedel-Crafts alkylation reaction under thermal condition (scheme 1.30) [57, 58]. These types of reactions are alternative to typical Friedel-Crafts approach that suffers many drawbacks including product isomerization, disproportionation, overalkylation, extreme sensitivity to trace of water, rate of mixing, etc.



Scheme 1.30 *N*-Nitrosoamide mediated benzylation of benzene and toluene

1.8.4 Reduction of *N*-nitrosamides with sodium borohydride

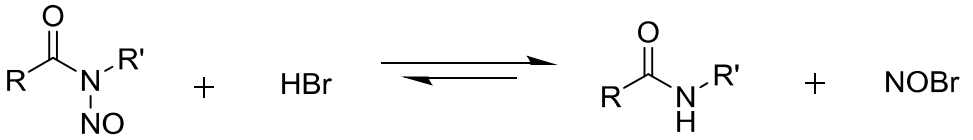
Reduction of carboxylic acids, esters, and amides are generally difficult with sodium borohydride. In this context, Rudinger *et al.* (1955) reported the reduction of secondary amides with $NaBH_4$ *via* *N*-nitrosamide intermediate at room temperature (scheme 1.31) [59].



Scheme 1.31 Reduction of *N*-nitrosamide

1.8.5 Decomposition of *N*-nitrosamides by acid catalysts

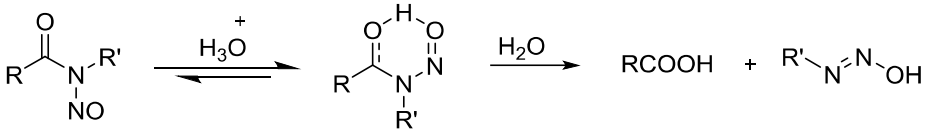
On treatment with gaseous HBr in organic solvents, *N*-nitrosamides regenerate the parent amide in quantitative yield. This implies that *N*-nitrosamide formation is reversible and explains why it is beneficial to add one mole of base (usually NaOAc) when synthesizing *N*-nitrosamides from amides and nitrosyl gases (scheme 1.32) [60].



Scheme 1.32 Acid catalyzed decomposition of *N*-nitrosamide

1.8.6 Hydrolysis of *N*-nitrosamide to carboxylic acid

N-Nitrosamides can easily be hydrolysed to corresponding carboxylic acids with aqueous acid. For example, *N*-nitrosamides undergo concurrent denitrosation and deamination in aqueous H_2SO_4 to give corresponding carboxylic acids (scheme 1.33) [60-62].



Scheme 1.33 Acid catalyzed hydrolysis of *N*-nitrosamide

1.9 Conclusion

The above discussion provides the significance of nitroso compounds in various fields. *N*-Nitrosamines have specific mutagenic and carcinogenic properties which induce cancers in animals. Besides being biologically important, *N*-nitrosamine compounds have become valuable intermediates in organic synthesis. Recently, *N*-nitrosamine functional groups have emerged as traceless directing groups for the activation of inert C-H bonds in aryl rings by associating with transition metals. In this context, our interest was to further explore the chemistry of *N*-nitroso compounds in different organic transformations.

1.10 The objectives of the thesis work

Our objective was to prepare or use *N*-nitrosamines and *N*-nitrosamides intermediates in organic synthesis. Under this topic, we have achieved the following transformations in an efficient manner-

1. Potassium persulfate promoted *N*-nitrosation of secondary and tertiary amines with nitromethane under mild condition.
2. *tert*-Butyl nitrite mediated nitrogen transfer reactions: synthesis of benzotriazoles and azides at room temperature
3. *tert*-Butyl nitrite catalyzed synthesis of benzimidazoles from *o*-phenylenediamine and aldehydes room temperature.
4. *tert*-Butyl nitrite promoted transamidation of secondary amides under metal and catalyst free condition.

These transformations are highly selective and efficient that provides the desired products in excellent yields.

1.11 References

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